

(19)



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(11)

EP 0 983 238 B1

(12)

EUROPEAN PATENT SPECIFICATION(45) Date of publication and mention
of the grant of the patent:**18.08.2004 Bulletin 2004/34**(21) Application number: **98922398.7**(22) Date of filing: **18.05.1998**(51) Int Cl.7: **C07D 211/34**(86) International application number:
PCT/US1998/010131(87) International publication number:
WO 1998/052921 (26.11.1998 Gazette 1998/47)(54) **PROCESSES AND INTERMEDIATES FOR RESOLVING PIPERIDYL ACETAMIDE
STEREISOISOMERS**VERFAHREN UND ZWISCHENPRODUKTE ZUR TRENNUNG VON
PIPERIDYLACETAMID-STEREISOISOMERENPROCEDES ET INTERMEDIAIRES POUR RESOUDRE DES STEREOISOMERES DE PIPERIDYL
ACETAMIDE(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE**(30) Priority: **22.05.1997 US 861988**(43) Date of publication of application:
08.03.2000 Bulletin 2000/10(60) Divisional application:
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US-A- 2 957 880

- **DEUTSCH H M ET AL: "SYNTHESIS AND PHARMACOLOGY OF POTENTIAL COCAINE ANTAGONISTS. 2. STRUCTURE-ACTIVITY RELATIONSHIP STUDIES OF AROMATIC RING-SUBSTITUTED METHYLPHENIDATE ANALOGS" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 39, 15 March 1996 (1996-03-15), pages 1201-1209, XP000602079 ISSN: 0022-2623**
- **JURSIC et al., "Determination of Enantiomeric Composition of 2-Phenyl-2-(2-Piperidyl)Acetamide. A Routine Method for Evaluation of Enantiomeric Purity of Primary Amides", TETRAHEDRON: ASSYMMETRY, 1994, Vol. 5, No. 9, pages 1711-1716, XP002910411**
- **BERRANG et al., "Enantiomeric alpha-Aminopropiophenones (Cathinone):Preparation and Investigation", 1982, Vol. 47, pages 2643-2647, XP002910412**
- **CHEMICAL ABSTRACTS, Vol. 104, No. 21, 26 May 1986, (Columbus, Ohio, USA), page 608, Abstract No. 186157a, OHASHI et al., "Acyl(Amino)Naphthalene Derivatives"; XP002910413; & JP,A,60 166 650 (29-08-85).**
- **CHEMICAL ABSTRACTS, Vol. 118, No. 11, 15 March 1993, (Columbus, Ohio, USA), page 805, Abstract No. 101538s, VANDERPLAS et al., "A Convenient Synthesis of Cis-(1R)-N-Benzyl(2S)-(Hydroxymethyl)Cyclohexylamine"; XP002910414; & ORG. PREP. PROCED. INT., 1992, 24(6), 685-7 (Eng.).**

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- PATRICK et al., "Synthesis of Deuterium Labelled Methylphenidate, P-Hydroxymethylphenidate, Ritalinic Acid and P-Hydroxyritalinic Acid", J. LABELLED COMP. AND RADIOPHARM., 1982, Vol. IX, No. 4, pages 485-490, XP002910415

Description**FIELD OF THE INVENTION**

[0001] This invention is directed to novel processes for resolution of piperidyl acetamide stereoisomers.

BACKGROUND OF THE INVENTION

[0002] Substituted piperidines have found use in the treatment of many nervous system disorders. For example, methylphenidate has been used to treat Attention Deficit Disorder (ADD), Attention Deficit Hyperactivity Disorder (ADHD) and cognitive decline in Acquired Immunodeficiency Syndrome (AIDS) and AIDS Related Complex (ARC) patients. (See, e.g., Greenhill, *Child & Adol. Psych. Clin. N.A.*, **1995**, 4, 123, and Brown, *Intl. J. Psychl. Med.*, **1995**, 25, 21).

[0003] Many currently available synthetic routes to methylphenidate and other substituted piperidines involve preparation of racemic mixtures. (See, e.g., U.S. Patent 2,507,631, to Hartmann, *et al.*, and U.S. Patent 2,957,880, to Rometsch, *et al.*). There are, however, a number of disadvantages associated with racemic mixtures of such drugs. Current administration of racemic methylphenidate often results in notable side effects such as anorexia, weight loss, insomnia, dizziness and dysphoria. Additionally, racemic methylphenidate produces a euphoric effect when administered intravenously or through inhalation, and thus carries a high potential for substance abuse in patients.

[0004] U.S. Patent Nos. 2,507,631 and 2,957,880 disclose synthetic procedures wherein methylphenidate, alternatively known as methyl α -piperid-2-ylphenylacetate, is prepared through a multi-step process in which 2-chloropyridine and phenylacetonitrile initially are coupled to form α -pyrid-2-ylphenylacetonitrile. The resulting α -pyrid-2-ylphenylacetonitrile then is hydrated in the presence of acid to yield α -pyrid-2-ylphenylacetamide which, in turn, is either: (a) catalytically hydrogenated to yield α -piperid-2-ylphenylacetamide and then converted to methyl α -piperid-2-ylphenylacetate, or (b) converted to methyl α -pyrid-2-ylphenylacetate which, in turn, is hydrogenated to yield methyl α -piperid-2-ylphenylacetate.

[0005] In the first embodiment of U.S. Patent No. 2,507,631 and in the process described in U.S. Patent No. 2,957,880, α -piperid-2-ylphenylacetamide is first separated into the *threo* and *erythro* diastereomeric racemates. This is accomplished through evaporation of the solvent utilized in the hydrogenation (*i.e.*, acetic acid), addition of sodium hydroxide to precipitate the α -piperid-2-ylphenylacetamide free base, recrystallization of this amide from ethyl acetate, and preferential crystallization of the *erythro* form by passing gaseous hydrogen chloride through an ethanolic solution of the amide.

[0006] The isolated *erythro* racemate then is resolved through formation of the *l*-tartrate salt, repeated recrystallizations of this salt from 96% ethanol are performed until a constant rotation is obtained, and the *l*-*erythro* form of α -piperid-2-ylphenylacetamide is precipitated with sodium hydroxide. The *l*-*erythro* form of α -piperid-2-ylphenylacetamide thus obtained is said to be subjected to epimerization to yield the desired *d*-*threo* diastereomer of α -piperid-2-ylphenylacetamide through treatment with 6 M potassium hydroxide. According to the disclosed procedure, the α -piperid-2-ylphenylacetamide thus obtained is converted to *d*-*threo* methyl α -piperid-2-ylphenylacetate through hydrolysis and esterification.

[0007] Some in the art have raised doubts as to whether the procedures disclosed in U.S. Patent Nos. 2,507,631 and 2,957,880 do, in fact, produce the desired *d*-*threo* isomer. Indeed, J.R. Soares, "Stereochemical Studies On Potential Central Nervous System Active Agents and Studies On The Chemistry Of Some 3-Benzoylpiperidines," 1971, Columbia University Ph.D. dissertation, p. 115, discloses that "all attempts to epimerize the resolved *erythro*-amides to the corresponding *threo*-amides by the procedure outlined in [U.S. 2,957,880] failed completely."

[0008] In any event, the synthetic procedure described in U.S. Patent Nos. 2,507,631 and 2,957,880 is wasteful in that it involves discarding the *threo* α -piperid-2-ylphenylacetamide racemate which is isolated following the recrystallization step and which typically represents approximately 25% of the acetamide product obtained via hydrogenation.

[0009] Consequently, there remains a need in the art for alternative synthetic procedures for the preparation of methylphenidate and other substituted piperidines. In particular, there is a need for synthetic procedures that do not require separating and discarding *threo* stereoisomers from the hydrogenation reaction product.

OBJECTS OF THE INVENTION

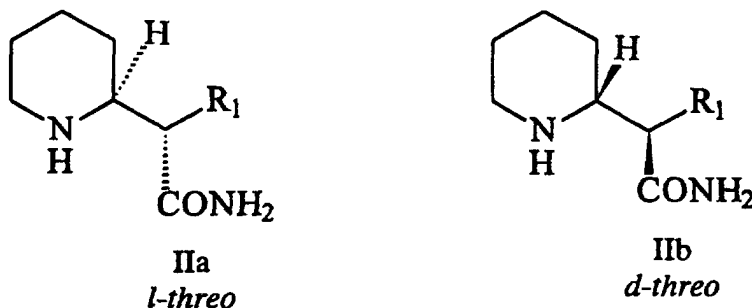
[0010] It is an object of the present invention to provide processes for the preparation of substituted piperidines.

[0011] It is another object of this invention to provide processes that provide synthetic intermediates and, hence, products having high optical purity.

[0012] It is yet another object to provide processes that proceed more efficiently than the processes disclosed by the prior art.

SUMMARY OF THE INVENTION

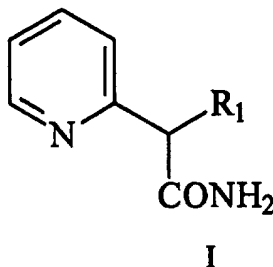
[0013] These and other objects are satisfied by the present invention, which provides processes for preparing piperidyl acetamides. In preferred embodiments, the processes of the invention comprise reacting *d,l*-threo piperidyl acetamide stereoisomers having formulas IIa and IIb:



(R₁ = aryl having about 6 to about 28 carbon atoms) with dibenzoyl-D-tartaric acid in an organic solvent comprising isopropanol, thereby forming acid salts of the *d*-threo stereoisomers preferentially with respect to the *l*-threo stereoisomers. The resulting acid salts then are reacted with aqueous base to form the corresponding piperidyl acetamide, which subsequently is converted to a corresponding ester.

DETAILED DESCRIPTION OF THE INVENTION

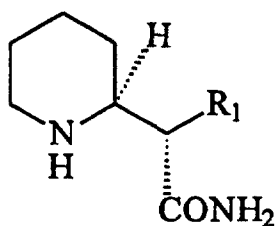
[0014] This invention provides novel processes for stereoselective synthesis of a variety 2-substituted piperidine stereoisomers. In one aspect, the invention is directed to synthetic methods involving hydrogenation of pyridines having formula I:



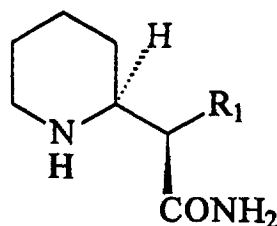
wherein R, is aryl having about 6 to about 28 carbon atoms. Aryl groups, as used herein, are aromatic groups containing a delocalized π -electron cloud. Such aromatic groups can be substituted with one or more substituents, such as, for example, halo, alkyl, aryl, hydroxy, alkoxy, carboxy, and cycloalkyl. Exemplary aryl groups include phenyl, naphthyl, xyl, chlorophenyl, fluorophenyl, trifluoromethylphenyl, and bromophenyl. Phenyl groups are preferred.

[0015] This hydrogenation can be effected by any of the numerous techniques known in the art. One preferred hydrogenation technique involves reacting the pyridine with hydrogen gas in the presence of a suitable catalyst in an alkanolic acid having 1 to about 10 carbon atoms. The hydrogenation preferably run at 25 °C and 40 psi. Representative catalysts contain platinum, with platinum oxide being particularly preferred. One preferred alkanolic acid is acetic acid.

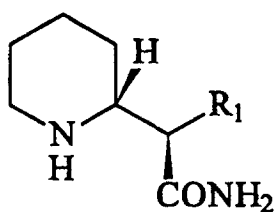
[0016] Hydrogenation of pyridine I provides a mixture of piperidine diastereomers IIa-d:



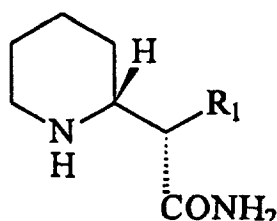
IIa
l-threo



IIc
d-erythro



IIb
d-threo



IIId
l-erythro

In accordance with the present invention, this mixture is treated with an organic base in an organic solvent to epimerize the *erythro* stereoisomers into *threo* forms. The epimerization can, for example, be effected in an aromatic hydrocarbon solvent such as toluene using an alkali metal alkoxide such as potassium *tert*-butoxide. In preferred embodiments, the epimerization is effected at 70 °C in an aromatic hydrocarbon solvent such as toluene using two equivalents of an alkali metal alkoxide such as potassium *tert*-butoxide.

[0017] The resulting composition, which should consist predominantly of *d,l-threo* piperidyl acetamide stereoisomers, is reacted with dibenzoyl-D-tartaric acid in an organic solvent comprising isopropanol, thereby forming acid salts of the *d-threo* stereoisomers preferentially with respect to the *l-threo* stereoisomers. Alkyl groups according to the invention are hydrocarbons which are straight, branched, or cyclic. Such hydrocarbons can be substituted with one or more substituents, such as, for example, halo, hydroxy, alkoxy, and carboxy groups. Exemplary alkyl groups include methyl, ethyl, isopropyl, *n*-butyl, *t*-butyl, *n*-pentyl, acetyl, trifluoromethyl, chloromethyl, and hexyl groups. The reaction of piperidyl acetamide stereoisomers with acid resolving agents preferably is performed with stirring at room temperature.

[0018] The acid resolving agent is dibenzoyl-D-tartaric acid, which is useful for forming *d-threo* stereoisomers preferentially with respect to *l-threo* isomers.

[0019] The piperidyl acetamide stereoisomers having formulas IIa and IIb can be reacted with an acid resolving agent in an organic solvent to form acid salts of the *l-threo* stereoisomers preferentially with respect to the *d-threo* stereoisomers. Resolving agents believed to be useful for forming *l-threo* stereoisomers preferentially with respect to *d-threo* isomers include (-)-dibenzoyl-L-tartaric acid. Crystallization preferably is performed at ambient temperature.

[0020] The acid salts obtained via resolution typically are dissolved in water and treated with an aqueous base such as a carbonate, bicarbonate, or hydroxide to precipitate the corresponding piperidyl amide free base in substantially pure form. They then can be reacted with an alcohol having, for example, 1 to about 5 carbon atoms in the presence of acid to form the corresponding ester.

[0021] Additional advantages of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are not intended to be limiting.

Example 1

Preparation of *d*-Threo-methylphenidate Hydrochloride Via Diastereomeric Separation and Resolution of *d,l*-erythro-Amide (Comparative Example)A. α -Phenyl- α -pyridyl-(2)-acetonitrile

[0022]

Materials:	
2-Chloropyridine (99%)	286 g (2.50 moles)
Benzyl cyanide (98%)	314 g (2.62 moles)
Sodium amide (90%)	217 g (5.00 moles)
Toluene	0.98 + 0.17 L
Water	0.87 L
Ethyl acetate	0.43 L
Hexanes	1.56 + 1.95 L
Brine	0.43 L

Procedure:

[0023] A 5L multi-neck glass reactor was charged with 2-chloropyridine, benzyl cyanide, and toluene (0.98 L). Sodium amide powder was added over a 1h period via a solid-addition funnel, keeping the reaction temperature below 30°C. The reaction mixture was stirred for 16h at ambient temperature. The reaction was then cooled to ~ 10°C, and quenched with 0.87 L water. Ethyl acetate (0.43 L) was added to solubilize the precipitated product. The organic layer was separated and washed once with 0.43 L brine. Solvent was removed from the organic layer on a rotovap, and toluene (0.17L), followed by hexanes (1.56 L), were added to the resulting residue. The resulting slurry was filtered. The filter cake was washed with hexanes (1.95 L), and dried to give 441 g of α -phenyl- α -pyridyl-(2)-acetonitrile as light brown crystals (90% yield based on 2-chloropyridine).

B. α -Phenyl- α -pyridyl-(2)-acetamide

[0024]

Materials:	
α -Phenyl- α -pyridyl-(2)-acetonitrile	441 g (2.27 moles)
Cone. H ₂ SO ₄	0.55 L
Water	1.63 L
50% NaOH	1.27 L

Procedure:

[0025] The reactor was charged with conc. H₂SO₄, and cooled to ~ 10°C. α -Phenyl- α -pyridyl-(2)-acetonitrile (from Example 1.A) was added portionwise, keeping the temperature below 30°C. The reaction was stirred at ambient temperature for 16h. The reaction mixture then was cooled to 10°C, at which point water was added. The NaOH then was added to a pH of 12, keeping the temperature below 30°C. The resulting crystals were filtered, and the filter cake was washed with water and dried under vacuum to give 482 g (100%) of α -phenyl- α -pyridyl-(2)-acetamide.

[0026] NH₄OH can be substituted for NaOH to adjust the pH to 12. One advantage of using NH₄OH is that the by-product that is formed (ammonium sulfate) is more soluble in water than the by-product (sodium sulfate) formed when NaOH is used as the base. Thus, the product crystals are less likely to be contaminated with inorganic salts.

C. *d,l*-erythro- α -Phenyl- α -piperidyl-(2)-acetamide**[0027]**

Materials:	
α -Phenyl- α -pyridyl-(2)-acetamide	482 g (2.27 moles)
Platinum oxide (PtO ₂)	8.06 g
Acetic acid	1.68 + 4.13 L
Celite	500 + 250 g
Ethyl acetate	3.10 + 0.62 + 2.07 + 2.07 + 4.13 + 0.21 L
Water	4.13 + 1.03 + 2.07 L
50% NaOH	0.56 L

Procedure:

[0028] The reactor was charged with α -phenyl- α -pyridyl-(2)-acetamide (from Example 1.B), acetic acid (1.68 L), and PtO₂. The reactor then was filled with hydrogen gas, and pressurized to 60 psi. The reaction mixture was hydrogenated at room temperature for 16h. The reaction mixture was filtered through a pad of Celite (500 g) to remove catalyst, and the Celite pad washed with acetic acid (4.13 L). The filtrate was concentrated under reduced pressure. Ethyl acetate (3.10 L) was added to the residue and stirred for 2h. The resulting crystals (first crop) were filtered, washed with ethyl acetate (0.62 L), and dried. The filtrate was concentrated under reduced pressure. Ethyl acetate (2.07 L) was added to the residue and stirred for 2h. The resulting crystals (second crop) were filtered, washed with ethyl acetate (2.07 L), and dried. The crystals from first and second crops were combined and dissolved in water (4.13 L), filtered through a pad of Celite (250 g), and the Celite pad was washed with water (1.03 L). The resulting filtrate was cooled to 10°C, followed by addition of 50% NaOH until the pH of the mixture was 13 and the free amine crystallized out. The crystals were filtered, washed with water (2.07 L), and dried to give 297 g (60%) of *d,l*-erythro- α -phenyl- α -piperidyl-(2)-acetamide.

D. *l*-erythro- α -Phenyl- α -piperidyl-(2)-acetamide**[0029]**

Materials:	
<i>d,l</i> -erythro- α -phenyl- α piperidyl-(2) -acetamide	297.2 g (1.361 moles)
D-(-)-Tartaric acid	204.3 g (1.361 moles)
Methanol	7.13 + 7.13 L
Water	2.0 L
50% NaOH	0.1 L

Procedure:

[0030] D-(-)-Tartaric acid dissolved in methanol (7.13 L) was added to a stirred solution of *d,l*-erythro- α -phenyl- α -piperidyl-(2)-acetamide (from Example 1.C), dissolved in methanol (7.13 L). The resulting clear solution was stirred for 16h, whereby the tartrate salt of *l*-erythro-acetamide crystallized out. The crystals were filtered, washed with methanol and dried. This tartrate salt was dissolved in water and 50% NaOH was added to a pH of 12, whereby the free base precipitated out. The precipitated crystals were filtered, washed with water and dried to give 119 g (40%) of *l*-erythro- α -phenyl- α -piperidyl-(2)-acetamide.

E. *d-threo*- α -Phenyl- α -piperidyl-(2)-acetamide**[0031]**

Materials:	
<i>l-erythro</i> - α -phenyl- α -piperidyl-(2)-acetamide	119g (0.544 moles)
Potassium t-butoxide (95%)	141.5g (1.198 moles)
Toluene	3.57L
Water	0.60 + 0.30 + 1.20L
Conc. HCl	0.24 + 0.12L
50% NaOH	0.14L

Procedure:

[0032] A mixture of 1-erythro- α -phenyl- α -piperidyl-(2)-acetamide (from Example 1.D), potassium t-butoxide, and toluene was heated to 70°C and stirred for 16h. The reaction mixture was cooled to room temperature, followed by slow addition of water (0.60L). Conc. HCl (0.24L) was added to this resulting mixture, and stirred for 0.5 h. The layers were separated, and the top organic layer was washed with a prepared solution of conc. HCl (0.12L) and water (0.30L). The combined aqueous layers were cooled to 10°C, and 50% NaOH was added to a pH of 12, whereby the free base precipitated out. The crystals were filtered, washed with water (1.20L), and dried to give 101 g (85%) of *d-threo*- α -phenyl- α -piperidyl-(2)-acetamide.

F. *d-threo*-Methylphenidate Hydrochloride**[0033]**

Materials:	
<i>d-threo</i> - α -phenyl- α -piperidyl-(2)-acetamide	101 g (0.46 moles)
Conc. H ₂ SO ₄	121 mL
Methanol	1.1 L
Water	0.81 L
50% NaOH	175 mL
Diethyl ether	1.0 + 1.0 + 1.0 + 1.0 L
Magnesium sulfate	20 g
HCl gas	As needed.

Procedure:

[0034] A solution of *d-threo*- α -phenyl- α -piperidyl-(2)-acetamide (from Example 1.E) and conc. H₂SO₄ in methanol was heated to reflux and stirred for 2 days. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Water (0.81 L) and ether (1.0 L) were added to the residue. NaOH was added to a pH of 12, and the layers were separated. The aqueous layer was extracted with ether (1.0 L). MgSO₄ was added to the combined ether layers, filtered, and washed with ether (1.0 L). HCl gas was passed through the filtrate with stirring, whereby white crystals of *d-threo*-methylphenidate hydrochloride precipitated out. The crystals were filtered, washed with ether (1.0 L), and dried to give 100 g (80%) of *d-threo*-methylphenidate hydrochloride.

[0035] The overall yield for Example 1 was 14.7%.

Example 2

Preparation of *d*-Threo-methylphenidate Hydrochloride Via Epimerization and Resolution of *d,l*-Threo-amide EnantiomersA. α -Phenyl- α -pyridyl-2-acetonitrile

[0036]

Materials:	
2-Chloropyridine (99%)	172 g (1.50 moles)
Benzyl cyanide (98%)	188 g (1.576 moles)
Sodium amide (90%)	130 g (3.00 moles)
Toluene	0.59 + 0.10 L
Water	0.52 L
Ethyl acetate	0.26 L
Hexanes	0.94 + 1.17 L
Brine	0.26 L

Procedure:

[0037] The reactor was charged with 2-chloropyridine, benzyl cyanide, and toluene (0.59 L). Sodium amide powder was added over a 1h period via a solid-addition funnel, keeping the reaction temperature below 300°C. The reaction mixture was stirred for 16h at ambient temperature. The reaction was cooled to ~ 10°C, and quenched with 0.52 L water. Ethyl acetate (0.26 L) was added to solubilize the precipitated product. The organic layer was separated and washed once with 0.26 L brine, and solvent was removed from the organic layer on a rotovap. Toluene (0.10 L), followed by hexanes (0.94 L) were added to the resulting residue. The resulting slurry was filtered, and the filter cake was washed with hexanes (1.17 L), and dried to give 265 g of α -phenyl- α -pyridyl-(2)-acetonitrile as light brown crystals (90% yield based on 2-chloropyridine).

B. α -Phenyl- α -pyridyl-(2)-acetamide

[0038]

Materials:	
α -Phenyl- α -pyridyl-(2)-acetonitrile	264 g (1.362 moles)
Conc. H ₂ SO ₄	0.33 L (6.226 moles)
Water	0.98 L
50% NaOH	0.77 L

Procedure:

[0039] The reactor was charged with conc. H₂SO₄, and cooled to ~ 10°C. α -Phenyl- α -pyridyl-(2)-acetonitrile (from Example 2.A) was added portionwise, keeping the temperature below 30°C. The reaction was stirred at ambient temperature for 16h. The reaction mixture then was cooled to 10°C, the water was added, and the NaOH was added to a pH of 12, keeping the temperature below 30°C. The resulting crystals were filtered, the filter cake was washed with water, and dried under vacuum to give 289 g (100%) of α -phenyl- α -pyridyl-(2)-acetamide.

C. *d,l*-erythro/threo- α -Phenyl- α -piperidyl-(2)-acetamide**[0040]**

Materials:	
α -Phenyl- α -pyridyl-(2)-acetamide	289 g (1.365 moles)
Platinum oxide (PtO ₂)	4.84 g
Acetic acid	1.01 + 2.48 L
Celite	300 + 150 g
Water	2.48 + 0.62 + 1.24 L
50% NaOH	0.33 L

Procedure:

The reactor was charged with α -phenyl- α -pyridyl-(2)-acetamide (from Example 2.B), acetic acid (1.01 L), and PtO₂. The reactor then was filled with hydrogen gas, pressurized to 60 psi, and the mixture hydrogenated at room temperature for 16h. The reaction mixture then was filtered through a pad of Celite (300 g) to remove the catalyst, and the Celite pad is washed with acetic acid (2.48 L). The filtrate was concentrated under reduced pressure. The resulting residue was dissolved in water (2.48 L), filtered through a pad of Celite (150 g), and the Celite pad was washed with water (0.62 L). The resulting filtrate was cooled to 10°C, followed by addition of 50% NaOH until the pH of the mixture was 13 and the free amine crystallized out. The crystals were filtered, washed with water (1.24 L), and dried to give 297 g (100%) of a 4:1 mixture of *d,l*-erythro- α -phenyl- α -piperidyl-(2)-acetamide and *d,l*-threo- α -phenyl- α -piperidyl-(2)-acetamide.

D. *d,l*-threo- α -Phenyl- α -piperidyl-(2)-acetamide**[0042]**

Materials:	
Mixture of <i>d,l</i> -erythro-acetamide and <i>d,l</i> -threo-acetamide	297 g (1.36 moles)
Potassium t-butoxide (95%)	354 g (2.996 moles)
Toluene	8.92 L
Water	1.49 + 0.74 + 3.00 L
Conc. HCl	0.59 + 0.30 L
50% NaOH	0.36 L

Procedure:

A mixture of *d,l*-erythro-acetamide and *d,l*-threo-acetamide (from Example 2.C), potassium t-butoxide, and toluene was heated to 70°C and stirred for 16h. The reaction mixture was cooled to room temperature, followed by slow addition of water (1.49L). Conc. HCl (0.59L) was added to this resulting mixture, which was stirred for 0.5h. The layers were separated, and the top organic layer was then washed with a prepared solution of conc. HCl (0.30L) and water (0.74L). The combined aqueous layers were cooled to 10°C, and 50% NaOH was added to a pH of 12 whereby the free base precipitated out. The crystals were filtered, washed with water (3.00 L), and dried to give 253 g (85%) of *d,l*-threo- α -phenyl- α -piperidyl-(2)-acetamide.

E. *d*-threo- α -Phenyl- α -piperidyl-(2)-acetamide**[0044]**

Materials:	
<i>d,l</i> -threo- α -phenyl- α -piperidyl-(2)- acetamide	253 g (1. 159 moles)
Dibenzoyl-D-tartaric acid	415 g (1. 159 moles)

(continued)

Materials:	
Isopropanol	8.11 L
6N HCl (aqueous)	1.67 L
Water	1.0 L
Solid NaCl	290g
50% NaOH (aqueous)	1.0 L

Procedure:

[0045] Dibenzoyl-D-tartaric acid and *d,l-threo*- α -phenyl- α -piperidyl-(2)-acetamide (from Example 2.D) were dissolved in isopropanol by warming the reaction mixture to $\sim 50^{\circ}\text{C}$. The resulting clear solution was stirred at ambient temperature for 16h, whereby the tartrate salt of *d-threo*-acetamide crystallized out. The crystals were filtered, and the filter cake was washed with isopropanol and dried in a vacuum oven at 40°C . This tartrate salt was added in portions to a stirred solution of 6N aq. HCl, and the resultant slurry was stirred at ambient temperature for 4h. The slurry was filtered, and the filter cake (containing free dibenzoyl-D-tartaric acid) was washed with water. Solid NaCl was added to the filtrate (which contained *d-threo*-acetamide hydrochloride salt) and the mixture was cooled to $\sim 10^{\circ}\text{C}$. The NaOH was added to this mixture to a pH of 12, whereby the free base of *d-threo*-acetamide precipitated out. The precipitated crystals were filtered, washed with water and dried to give 101 g (40%) of *d-threo*- α -phenyl- α -piperidyl-(2)-acetamide.

F. *d-threo*-Methylphenidate Hydrochloride

[0046]

Materials:	
<i>d-threo</i> - α -phenyl- α -piperidyl-(2)-acetamide	101 g (0.46 moles)
Conc. H_2SO_4	121 mL
Methanol	1.1 L
Water	0.81 L
50% NaOH	175 mL
Diethyl ether	1.0 + 1.0 + 1.0 + 1.0 L
Magnesium sulfate	20 g
HCl gas	As needed.

Procedure:

[0047] A solution of *d-threo*- α -phenyl- α -piperidyl-(2)-acetamide (from Example 2.E) and conc. H_2SO_4 in methanol was heated to reflux and stirred for 2 days. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Water (0.81 L) and ether (1.0 L) were added to the residue. The NaOH was added to a pH of 12, and the layers were separated. The aqueous layer was extracted with ether (1.0 L). MgSO_4 was added to the combined ether layers, filtered, and washed with ether (1.0 L). HCl gas was passed through the filtrate with stirring, whereby white crystals of *d-threo*-methylphenidate hydrochloride precipitated out. The crystals were filtered, washed with ether (1.0 L), and dried to give 100 g (80%) of *d-threo*-methylphenidate hydrochloride.

[0048] In contrast to Example 1, the overall yield for Example 2 was 24.5%, an increase of over 66%.

Example 3

Preparation of *l*-Threo-methylphenidate Hydrochloride Via Epimerization and Resolution of *d,l*-Threo-amide EnantiomersA. α -Phenyl- α -pyridyl-2-acetonitrile

[0049]

Materials:	
2-Chloropyridine (99%)	172 g (1.50 moles)
Benzyl cyanide (98%)	188 g (1.576 moles)
Sodium amide (90%)	130 g (3.00 moles)
Toluene	0.59 + 0.10 L
Water	0.52 L
Ethyl acetate	0.26 L
Hexanes	0.94 + 1.17 L
Brine	0.26 L

Procedure:

[0050] The reactor was charged with 2-chloropyridine, benzyl cyanide, and toluene (0.59 L). Sodium amide powder was added over a 1h period via a solid-addition funnel, keeping the reaction temperature below 300°C. The reaction mixture was stirred for 16h at ambient temperature. The reaction was cooled to ~ 10°C, and quenched with 0.52 L water. Ethyl acetate (0.26 L) was added to solubilize the precipitated product. The organic layer was separated and washed once with 0.26 L brine, and solvent was removed from the organic layer on a rotovap. Toluene (0.10 L), followed by hexanes (0.94 L) were added to the resulting residue. The resulting slurry was filtered, and the filter cake was washed with hexanes (1.17 L), and dried to give 265 g of α -phenyl- α -pyridyl-(2)-acetonitrile as light brown crystals (90% yield based on 2-chloropyridine).

B. α -Phenyl- α -pyridyl-(2)-acetamide

[0051]

Materials:	
α -Phenyl- α -pyridyl-(2)-acetonitrile	264 g (1.362 moles)
Conc. H ₂ SO ₄	0.33 L (6.226 moles)
Water	0.98 L
50% NaOH	0.77 L

Procedure:

[0052] The reactor was charged with conc. H₂SO₄, and cooled to ~ 10°C. α -Phenyl- α -pyridyl-(2)-acetonitrile (from Example 3.A) was added portionwise, keeping the temperature below 30°C. The reaction was stirred at ambient temperature for 16h. The reaction mixture then was cooled to 10°C, the water was added, and the NaOH was added to a pH of 12, keeping the temperature below 30°C. The resulting crystals were filtered, the filter cake was washed with water, and dried under vacuum to give 289 g (100%) of α -phenyl- α -pyridyl-(2)-acetamide.

C. *d,l*-erythro/threo- α -Phenyl- α -piperidyl-(2)-acetamide**[0053]**

Materials:	
α -Phenyl- α -pyridyl-(2)-acetamide	289 g (1.365 moles)
Platinum oxide (PtO ₂)	4.84 g
Acetic acid	1.01 + 2.48 L
Celite	300 + 150 g
Water	2.48 + 0.62 + 1.24 L
50% NaOH	0.33 L

Procedure:

[0054] The reactor was charged with α -phenyl- α -pyridyl-(2)-acetamide (from Example 3.B), acetic acid (1.01 L), and PtO₂. The reactor then was filled with hydrogen gas, pressurized to 60 psi, and the mixture hydrogenated at room temperature for 16h. The reaction mixture then was filtered through a pad of Celite (300 g) to remove the catalyst, and the Celite pad is washed with acetic acid (2.48 L). The filtrate was concentrated under reduced pressure. The resulting residue was dissolved in water (2.48 L), filtered through a pad of Celite (150 g), and the Celite pad was washed with water (0.62 L). The resulting filtrate was cooled to 10°C, followed by addition of 50% NaOH until the pH of the mixture was 13 and the free amine crystallized out. The crystals were filtered, washed with water (1.24 L), and dried to give 297 g (100%) of a 4:1 mixture of *d,l*-erythro- α -phenyl- α -piperidyl-(2)-acetamide and *d,l*-threo- α -phenyl- α -piperidyl-(2)-acetamide.

D. *d,l*-threo- α -Phenyl- α -piperidyl-(2)-acetamide**[0055]**

Materials:	
Mixture of <i>d,l</i> -erythro-acetamide and <i>d,l</i> -threo-acetamide	297 g (1.36 moles)
Potassium t-butoxide (95%)	354 g (2.996 moles)
Toluene	8.92 L
Water	1.49 + 0.74 + 3.00 L
Conc. HCl	0.59 + 0.30 L
50% NaOH	0.36 L

Procedure:

[0056] A mixture of *d,l*-erythro-acetamide and *d,l*-threo-acetamide (from Example 3.C), potassium t-butoxide, and toluene was heated to 70°C and stirred for 16h. The reaction mixture was cooled to room temperature, followed by slow addition of water (1.49L). Conc. HCl (0.59L) was added to this resulting mixture, which was stirred for 0.5h. The layers were separated, and the top organic layer was then washed with a prepared solution of conc. HCl (0.30L) and water (0.74L). The combined aqueous layers were cooled to 10°C, and 50% NaOH was added to a pH of 12 whereby the free base precipitated out. The crystals were filtered, washed with water (3.00 L), and dried to give 253 g (85%) of *d,l*-threo- α -phenyl- α -piperidyl-(2)-acetamide.

E. *l*-threo- α -Phenyl- α -piperidyl-(2)-acetamide**[0057]**

Materials:	
<i>d,l</i> -threo- α -phenyl- α -piperidyl-(2)- acetamide	253 g (1. 159 moles)
Dibenzoyl-L-tartaric acid	415 g (1. 159 moles)

(continued)

Materials:	
Isopropanol	8.11 L
6N HCl (aqueous)	1.67 L
Water	1.0 L
Solid NaCl	290g
50% NaOH (aqueous)	1.0 L

Procedure:

[0058] Dibenzoyl-L-tartaric acid and *d,l*-*threo*- α -phenyl- α -piperidyl-(2)-acetamide (from Example 3.D) is dissolved in isopropanol by warming the reaction mixture to $\sim 50^{\circ}\text{C}$. The resulting clear solution is stirred at ambient temperature for 16h, whereby the tartrate salt of *l*-*threo*-acetamide crystallizes out. The crystals are filtered, and the filter cake washed with isopropanol and dried in a vacuum oven at 40°C . This tartrate salt is added in portions to a stirred solution of 6N aq. HCl, and the resultant slurry is stirred at ambient temperature for 4h. The slurry is filtered, and the filter cake (containing free dibenzoyl-L-tartaric acid) is washed with water. Solid NaCl is added to the filtrate (which contains *l*-*threo*-acetamide hydrochloride salt) and the mixture is cooled to $\sim 10^{\circ}\text{C}$. The NaOH is added to this mixture to a pH of 12, whereby the free base of *l*-*threo*-acetamide precipitates out. The precipitated crystals are filtered, washed with water and dried to give *l*-*threo*- α -phenyl- α -piperidyl-(2)- acetamide.

F. *l*-*threo*-Methylphenidate Hydrochloride

[0059]

Materials:	
<i>l</i> - <i>threo</i> - α -phenyl- α -piperidyl-(2)-acetamide	101 g (0.46 moles)
Conc. H_2SO_4	121 mL
Methanol	1.1 L
Water	0.81 L
50% NaOH	175 mL
Diethyl ether	1.0 + 1.0 + 1.0 + 1.0 L
Magnesium sulfate	20 g
HCl gas	As needed.

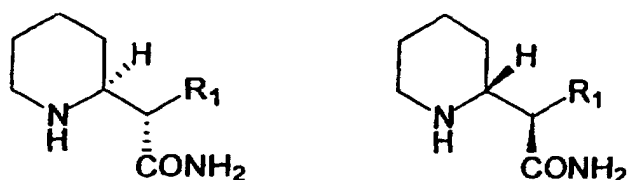
Procedure:

[0060] A solution of *l*-*threo*- α -phenyl- α -piperidyl-(2)- acetamide (from Example 3.E) and conc. H_2SO_4 in methanol is heated to reflux and stirred for 2 days. The reaction mixture is cooled to room temperature and concentrated under reduced pressure. Water (0.81 L) and ether (1.0 L) are added to the residue. The NaOH is added to a pH of 12, and the layers are separated. The aqueous layer is extracted with ether (1.0 L). MgSO_4 is added to the combined ether layers, filtered, and washed with ether (1.0 L). HCl gas is passed through the filtrate with stirring, whereby white crystals of *l*-*threo*-methylphenidate hydrochloride precipitate out. The crystals are filtered, washed with ether (1.0 L), and dried to give *l*-*threo*-methylphenidate hydrochloride.

Claims

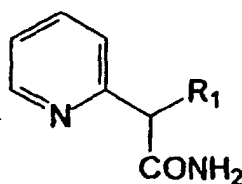
1. A synthetic process comprising the steps of:

providing *d,l*-*threo* piperidyl acetamide stereoisomers having formulas:

*L-threo**D-threo*

wherein R_1 is aryl having about 6 to about 28 carbon atoms; and reacting said stereoisomers with dibenzoyl-D-tartaric acid in an organic solvent comprising isopropanol, thereby forming acid salts of said *D-threo* stereoisomers preferentially with respect to said *L-threo* stereoisomers; and isolating said *D-threo* acid salts.

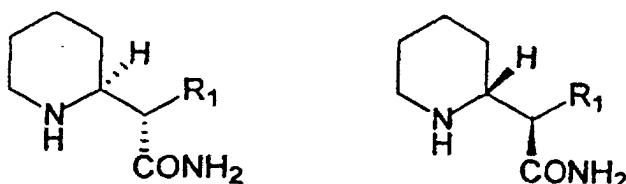
2. The process of claim 1 wherein R_1 is phenyl.
3. The process of claim 1 further comprising reacting said *D-threo* acid salts with aqueous base to form said *D-threo* piperidyl-acetamide.
4. The process of claim 3 further comprising reacting said *D-threo* piperidyl-acetamide with an alcohol having 1 to about 5 carbon atoms in the presence of acid to form a *D-threo* piperidine acetate.
5. The process of claim 1 wherein said *D,L-threo* piperidyl acetamide stereoisomers are prepared by reacting a pyridine having formula:



with hydrogen in an alkanolic acid having 1 to about 10 carbon atoms in the presence of a catalyst to provide a mixture of *threo* and *erythro* piperidyl stereoisomers; and contacting said *erythro* stereoisomers with organic base, thereby converting said *erythro* piperidyl stereoisomers to *threo* piperidyl stereoisomers.

Patentansprüche

1. Synthetisches Verfahren, das folgende Schritte aufweist, nämlich Bereitstellen von Stereoisomeren des *D,L-threo*-Piperidylacetamids mit den Formeln:

*L-threo**D-threo*

in denen R_1 Aryl mit etwa 6 bis etwa 28 Kohlenstoffatomen ist; und

Reagieren der Stereoisomere mit Dibenzoyl-D-weinsäure in einem organischen Lösemittel, das Isopropanol aufweist, wobei Säuresalze der *d-threo*-Stereoisomere bevorzugt gegenüber den *l-threo*-Stereoisomeren gebildet werden und

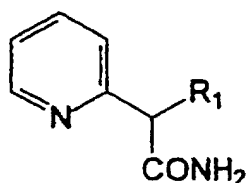
Isolieren der *d-threo*-Säuresalze.

2. Verfahren nach Anspruch 1, wobei R_1 Phenyl ist.

3. Verfahren nach Anspruch 1, das ferner das Reagieren der *d-threo*-Säuresalze mit wässriger Base aufweist, um das *d-threo*-Piperidylacetamid zu bilden.

4. Verfahren nach Anspruch 3, das ferner das Reagieren des *d-threo*-Piperidylacetamid mit einem Alkohol mit 1 bis etwa 5 Kohlenstoffatomen in Anwesenheit einer Säure aufweist, um ein *d-threo*-Piperidinacetat zu bilden.

5. Verfahren nach Anspruch 1, wobei die Stereoisomere des *d,l-threo*-Piperidylacetamids hergestellt werden durch Reagieren eines Pyridins mit der Formel:



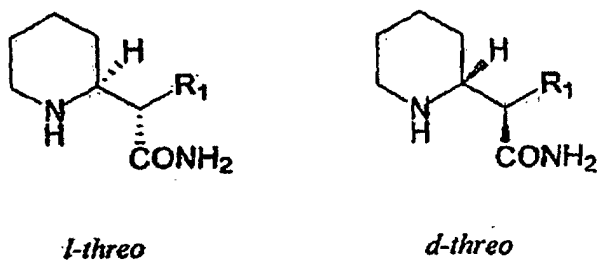
mit Wasserstoff in einer Alkansäure mit 1 bis etwa 10 Kohlenstoffatomen, und zwar in Anwesenheit eines Katalysators, um eine Mischung von *threo*- und *erythro*-Piperidyl Stereoisomeren bereitzustellen; und

In-Berührung-Bringen der *erythro*-Stereoisomere mit organischer Base, wodurch die *erythro*-Piperidyl Stereoisomere zu *threo*-Piperidyl Stereoisomeren umgewandelt werden.

Revendications

1. Procédé de synthèse comprenant les étapes qui consistent à :

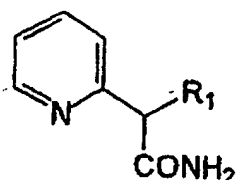
fournir des stéréo-isomères *d,l-threo* pipéridyl-acétamide répondant aux formules :



dans lesquelles R_1 représente un groupe aryle possédant d'environ 6 à environ 28 atomes de carbone ; et faire réagir lesdits stéréo-isomères avec l'acide dibenzoyl-D-tartrique dans un solvant organique comprenant de l'isopropanol pour former ainsi préférentiellement des sels acides desdits stéréo-isomères *d-threo* par rapport auxdits stéréo-isomères *l-threo* ; et isoler lesdits sels acides *d-threo*.

2. Procédé selon la revendication 1, dans lequel R_1 représente le groupe phényle.

3. Procédé selon la revendication 1, qui comprend en outre la réaction desdits sels acides d-thréo avec une base aqueuse pour former ledit d-thréo pipéridyl acétamide.
4. Procédé selon la revendication 3, qui comprend en outre la réaction dudit d-thréo pipéridyl acétamide avec un alcool possédant de 1 à environ 5 atomes de carbone en présence d'acide pour former un d-thréo pipéridine acétate.
5. Procédé selon la revendication 1, dans lequel on prépare lesdits stéréo-isomères d,l-thréo pipéridyl-acétamide par réaction d'une pyridine répondant à la formule :



avec de l'hydrogène dans un acide alcanoïque possédant de 1 à environ 10 atomes de carbone en présence d'un catalyseur pour fournir un mélange des stéréo-isomères thréo et érythro pipéridyle ; et
par la mise en contact desdits stéréo-isomères érythro avec une base organique pour transformer ainsi lesdits stéréo-isomères érythro pipéridyle en stéréo-isomères thréo pipéridyle.